REMARKS

Applicants have given the Examiner's comments very careful consideration. Claims 7-9 have been cancelled for the purpose of expediting prosecution. Claims 1 and 4 have been amended. The amendatory language introduced into claim 1, *i.e.*, "determining the weight of a patient diagnosed with cancer," while believed to be redundant with the recitation "determining a therapeutically effective dose of arsenic trioxide based on the weight of a patient," reinforces what Applicants mean by, and what has come to be understood in the art as "weight based" dosing of arsenic trioxide.

The Office action is surprisingly silent with respect to the vast majority of the arguments and evidence previously submitted, except to state that the Ellison declaration was "irrelevant" because it deals with methods, whereas the claims are directed to kits. This viewpoint is clearly wrong -- claims 1-6 are not new claims. Accordingly, Applicants have reiterated their previous arguments, including those based on the Ellison declaration. The Examiner is urged to conduct a complete review of this Amendment, and to consider Applicants' arguments and evidence in their entirety.

Applicants believe that claim 1-6, directed to methods of treating cancer or determining a dose of ATO to treat cancer, by administering ATO, and which recite determining a therapeutically effective dosage amount of arsenic trioxide based upon the weight of a patient, define a patentable contribution over the prior art.

The Office Action states that the rejection of claims 1-9 under 35 U.S.C. § 103(a) over *Zhang* or *Chen*, and that the obviousness rejection based upon *Yang* are being maintained to reject claims 1 and 7-9. Since claims 7-9 have been cancelled,

Applicants will address the rejections to the extent that they still apply to claims 1-6 and 1 respectively.

The Examiner's position is that the disclosures in *Zhang* of a range of arsenic trioxide (ATO) of 1-10 mg, and the administration of smaller doses of ATO to children, suggest that that ATO can be administered according to a subject's body weight, and that the range amount actually administered had to be determined based on the body weight of the subject. Applicants disagree.

By way of summary, the invention disclosed in *Zhang* is directed to an intravenous pharmaceutical composition for the treatment of cancers, particularly types of leukemia such as APL and acute myeloid leukemia (AML), with a composition comprising ATO, sodium chloride, and water, and more particularly a composition containing 1 g - 10 g ATO, 8 g of sodium chloride and 1000 mL of sterile water. See, col. 1, lines 33-35 and 41-46. The only disclosure in *Zhang* regarding the actual dosage amount to administer to a patient may be found on column 2, lines 9-11 and 14-16, wherein *Zhang* teaches that an effective daily dose for an adult has been found to be 10 mL of a composition containing 10 g/L of ATO added to 500 mL of a 10% glucose solution, and that the amount of the composition used should be adjusted based on the concentration of the arsenic trioxide in the composition. Accordingly, *Zhang* teaches a *single* flat dose of 10 mL of a particular composition. Ten milliliters of a composition containing 10 g of arsenic trioxide in 500 mL of solution equates to the 10 mg flat dose, and thus is consistent with the other cited publications such as *Chen*. The disclosure in lines 14-16 indicates that more of less of *Zhang's* composition would be administered in order to achieve a flat dosage of 10 mg.

In the "EXAMPLE" on columns 2-3, *Zhang* summarizes treatment of 110 subjects diagnosed with APL, ranging from 13 to 65 years old (*Zhang*, col. 2, lines 60-62), and thus included both children and adults. Treatment entailed administration of the "composition of the invention for 2-4 weeks". Col. 3, lines 6-7. Notwithstanding the statement on col. 2, lines 16-17 (*i.e.*, that the appropriate dose should be decreased accordingly for children), the EXAMPLE contains no mention of administering a decreased dose of the ATO composition to the children who were treated.

Initially, therefore, it must be stated in the record that *Zhang* does not actually provide an example of administering a relatively small dose of ATO to children. In addition, even if one of ordinary skill in the art would be motivated to follow *Zhang's* teaching that the appropriate dose of ATO should be decreased for children, the claimed invention would still not be suggested or necessarily produced.

The claimed method requires dosing ATO on a weight basis, which as defined in the specification, involves determining the weight of a patient and then calculating a therapeutically effective dosage of ATO based on the weight. As illustrated on the working example beginning on page 29, the determination of the therapeutically effective dosage involves multiplying the weight of the patient by a predetermined dosage amount per unit weight, *Zhang* makes no such suggestion, as evidenced by his working example wherein both adults and children appear to be dosed with exactly the same amount of ATO. Moreover, if one skilled in the art adjusted the dose for children, there is no suggestion that weight would be the proper criteria for such adjustment. Simply put, reducing the dose for children does not equate to or suggest <u>weight based dosing</u> as required by the claimed methods.

Ironically, as set forth in the present application, in the course of developing their claimed invention applicants did exactly what *Zhang* suggested but did not do himself -- they actually experimented with decreasing the flat dose of ATO for administration to children. They found out, however, that the results were unacceptable. The prior response and Declaration by Dr. Ellison elaborate on this aspect of their work, and how the claimed invention provided unexpected results compared to flat dosing, or to arbitrary reductions in dosing for children as mentioned in *Zhang*. Unfortunately, the Office action does not address these arguments and evidence.

Accordingly, Applicants reiterate the arguments set forth on pages 11-12 of the prior response. As described in the present specification beginning on page 29, in the course of developing a clinical protocol for treatment of APL with ATO, the present inventors also initially adopted a flat-dosing approach. For their first five patients, applicants adopted the gold standard taught in the prior art, namely the daily 10-mg dose.

Alarmingly, Patient 5 in the initial group relapsed within 24 days of achieving total remission and before completion of the consolidation therapy. As the patient was a very large individual (163 kg), the inventors questioned whether he might have received too little drug at a flat dose of 10 mg daily. This observation of patient size as impacting efficacy in treatment of cancer with ATO is unprecedented in the prior art. The relevant literature did not suggest this problem or perspective, since there was no teaching that the size of a patient should be considered in arriving at an effective dosage. See also, ¶ 8 of the Ellison declaration.

When faced with an issue of under-dosing (efficacy), the inventors did not immediately conceive of weight-based

dosing, as claimed herein. Instead, the inventors sought to adjust the dose of arsenic trioxide to ascertain a proper flat dose for all patients. This approach was still consistent with the teachings of the prior art which provided arsenic trioxide to all patients in an equal amount.

Accordingly, since the drug had been well tolerated (*i.e.*, was safe) at 10 mg per day by the 5 initial patients, and in order to avoid the possibility of under dosing as was believed to have occurred with Patient 5, the dose was increased to a 15 mg flat dose for all subsequent patients. It was predicted that this dosage amount would still be safe for all patients and still be effective for larger patients. This dosage amount was given to Patients 6 and 7.

Importantly, it was recognized that arsenic trioxide is a deadly poison and is used as rat poison. Even with the difficulties encountered in treating patient 5, it was not postulated that it would be both safe and effective to meter the dose given to a patient directly to the weight of that patient, as has been asserted as obvious by the Examiner. Instead, the inventors deliberately adhered to the teachings of the prior art in order to find a flat dose that would not kill their patients but would still be effective against the disease.

Despite these efforts, the inventors were soon confronted with a new problem—that being toxicity. Patient 8 was a 13 year-old girl and was of smaller stature. To be cautious not to kill the girl with arsenic trioxide, therefore, the inventors chose to adjust the flat dose again and revert to the original, 10 mg-daily dose, for this patient. Patient 9 was a 9 year-old boy and, because of his size, was given a further adjusted flat dose of only 5 mg daily. Patient 10 was given the new standard dose of 15 mg daily. See also, Table 3 on page 41 of the present specification, and ¶9 of the Ellison declaration.

It must be appreciated that adjusting the flat dose is not weight based dosing, as that term is defined in the claims. The dosing as taught by the prior art, as in *Zhang*, has a defined upper limit of the amount of ATO that can be administered without killing the patient, *i.e.*, 10 mg/day. On the other hand, the methodology of the present invention has no such limit and in fact, was conceived to provide administration of greater amounts of ATO where appropriate. See, *e.g.*, paragraph 76 of the specification.

It is important to note that when faced with the problem of possibly of overdosing and killing a patient, a dose adjustment was made, but the adjustment was made on a flat-dose basis. The adjustment was not directly associated with the actual weight of the patient, as has been asserted as being obvious by the Examiner.

Upon reviewing the results for the first ten patients, the inventors ultimately concluded that the standard flat dosing method seemed not to be efficacious for large people and yet was too toxic for small people. Adjusting the dose to the size of the patient on a flat-dose basis as taught but not actually practiced by *Zhang* was considered to be unworkable.

The inventors then conceived of a method to dose arsenic trioxide directly in proportion to the weight of the patient. This approach is unprecedented for this chemical, and could have lead to life-threatening dosage levels for large patients and ineffective dosage levels for small people, regardless of their age. However, in practice this approach turned out to be unexpectedly safe and successful.

The experiment resulted in an understanding that this chemical can be delivered to patients directly in proportion to their weight.

The unexpected and substantial success of the claimed invention is further illustrated by several post-filing publications presented by authors fully aware of the teachings of the present patent application. This evidence shows, among other things, that applicants deviated from the conventional wisdom in the art and the "gold standard approach" of administering ATO on a flat dose basis, and achieved unexpected results. It also shows that persons in the field remained skeptical and in fact, were rather incredulous that the present invention worked - safely and effectively.

More specifically, post-filing reports by third parties evidence a persisting concern over toxicity in connection with the weight-based dosing regimens that had begun to be evaluated.

For example, the Westervelt group reported the results of another of its studies to determine, in the context of treating relapsed or refractory APL, the maximum tolerated dose or the minimum effective dose of ATO, thereby further to illuminate efficacy at that dose and to delineate the acute and chronic toxicities of ATO. Westervelt, *et al.*, Blood *98(2)*:266-71 (2001)(PTO-1449, page 4, CS2).

Once again, the study design entailed a weight-based dosing scheme, this time beginning at a dose of 0.10 mg/kg and increasing in increments of 0.05 mg/kg per day (page 267, left column). The study was curtailed at the initial 0.10 mg/kg per day, however, on account of three unexplained deaths, which the investigators suspected were due to arsenic-related cardiac arrhythmia. The (2001) Westervelt publication concludes with a warning to the effect that the deaths suggest high toxicity, associated with weight-based ATO dosages, and that until these issues were better defined, ATO should be used with caution.

Moreover, Westervelt, *et al.* concede that their results were in direct contrast with the results achieved in the trial reported in Soignet, *et al.* (2001) (*supra*) from the standpoint of the unexplained deaths (Soignet et al is the literature publication of the data presented in the present application). On the right column of page 270, they acknowledge that in the studies reported in *Soignet*, 52 patients were treated without any treatment-related deaths. While proffering various theories to explain the differing results, Westervelt, *et al.* reached no conclusions on this point.

Overall, the results achieved to date in connection with Applicants' claimed invention are in sharp contrast to the state of the art as evidenced by the Westervelt publication.

For example, in paragraph 11 of his declaration, Dr. Ellison states that between the time of the FDA approval for ATO (Trisenox®) and the time of the declaration, data already in the literature have been augmented by the results of treating an additional 2,228 patients with arsenic trioxide on a weight basis. To date, these additional results have included no reported deaths attributed to cardiac arrhythmia.

Yet other post-filing publications indicate that the claimed invention can be practiced, safely and effectively, in connection with other cancers. For example, Vey, "*Arsenic trioxide for the treatment of myelodysplastic syndromes,*" in Expert. Opin. Pharmacother. *5(3)*:613-621 (2004)(of record), reports the preliminary results of ongoing Phase II studies conducted in patients with myelodysplasia (MDS) using ATO administered on a weight basis *i.e.*, 0.25 mg/kg/day. The authors conclude that arsenic trioxide is a promising drug with a favorable toxicity profile:

> Arsenic trioxide is an old drug which has recently been rediscovered. The renewed attention on this compound has revealed its wide range of biological

> activities which support the rationale for its use in MDS, a disease for which no standard treatment has yet been established. The early results of the ongoing clinical studies confirm that arsenic trioxide has a favourable toxicity profile and can be administered on an out-patient basis in the MDS population which involves a majority of elderly patients. As previously reported in patients with APL, most of the adverse effects are non-chemotherapy-like, moderate and regress shortly after cessation of therapy.
>
> The efficacy assessment arsenic trioxide in MDS still rely on preliminary reports. However, the results of the different ongoing Phase II studies are consistent and some conclusions can be drawn: arsenic trioxide has clinical activity in MDS; the overall response rate is in the 25 – 30% range; the main clinical benefit is represented by HIs which can be observed across all haematological lineages; durable transfusion-independence can be achieved whereas complete or partial remission are anecdotal. These results thus indicate that arsenic trioxide is a promising drug for the treatment of MDS. Its favourable toxicity profile encourage the design of combined treatment strategies.

Vey, at page 618.

Positive results have also been reported in phase II studies with patients having relapsed or refractory multiple myeloma (MM). See, Hussein, *et al.*, "*Phase 2 study of arsenic trioxide in patients with relapsed or refractory multiple myeloma*," in Br. J. Haematol. *125*:470-76 (2004)(of record). Here, patients were administered 0.25 mg/kg/day of ATO for 5 days/week during the first two weeks of each 4-week cycle. According to the authors, the data indicate that arsenic trioxide is active and reasonably well tolerated as a single-agent salvage therapy, even in patients with late-stage, relapsed and refractory MM. (See abstract.) In fact, the authors suggest that weight-based ATO therapy might be preferable to chemotherapy in the management of this disease:

> Our findings highlight some important features in the clinical management of MM with arsenic trioxide when compared with chemotherapy. The increased incidence of neutropenia that was not associated with neutropenic fevers and not requiring intervention in the form of suspended therapy, reduced dose, growth factor use, or antibiotic therapy, is remarkable. Renal function was not compromised by arsenic trioxide therapy and actually improved during treatment in two patients with initially high serum creatinine levels. Overall, arsenic trioxide therapy did not compromise the patients' performance status and did not confer significant added toxicity."

Hussein, *et al.*, on page 474.

Lastly, as described in ¶12 of his declaration, Dr. Ellison explains that subsequent to the present invention, another group of oncologists chose to modify flat dosing to a dosing based upon the patient's size; this, in recognition of a need to protect patients from toxic doses of ATO during the APL treatment. See Au, *et al.*, Annals of Oncology *14*:752-57 (2003) (copy enclosed).

As an illustration that metering a dose of arsenic trioxide to the weight of a patient is not an obvious solution in adjusting a dose, in contrast to a weight-based dosing scheme, Au, *et al.* adopted a body surface area (BSA) dosing scheme, however. Thus, they described the use of BSA dosing in the context of treating a group of patient with relapsed APL. Initial treatment was on a flat-dosage basis for APL patients who underwent bone-marrow transplantation and ATO therapy. For double-relapse patients, however, the dosage was metered to take into account the size of the patient on a surface area basis. The difference in initial dosing and double-relapse dosing can only be interpreted as an acknowledgement of the need to balance toxicity and efficacy for the patients who had been weakened by extensive therapy beforehand. When faced with the same problem that the present inventors confronted, in other words,

Au, *et al*. resorted to more conventional treatment scheme, with dosing based upon patient surface area.

In conclusion, the evidence contained in the specification, as elaborated on by applicants in their prior response, as well as by Dr. Ellison, establish that arbitrary adjustments of flat doses of ATO to heavier adults and to children is not the same as or equivalent to weight-based dosing as required by the claimed invention, and that weight-based dosing would not have been obvious in view of any such arbitrary adjustments of flat dosing.

Nonetheless, in order to be complete and comprehensive in its treatment of the *Zhang* reference, applicants will now address the additional statements made by the Examiner on pages 2-3 of the Action. For example, at the bottom of page 2, the Examiner states that the "range amount of ATO (1-10 mg) administered *had to be determined* based on the body weight of the subject, the range amount taught by *Zhang* makes this obvious." This statement implies that the Examiner believes that the claimed invention would have been inherent based on this statement in *Zhang*. There is no actual teaching in *Zhang* of reduced dosing of ATO in children. In addition, inherency is irrelevant to the determination of obviousness.

Turning to the statement bridging pages 2-3, the Examiner is absolutely correct in stating that *Zhang* is not required to show treatment regimen using all points in his disclosed dose range of 1-10 mg of ATO. This fact actually weighs in favor of nonobviousness. Viewed from the collective teachings of the prior art, this is not surprising whatsoever. As laid out in the prior response, flat dosing of ATO in an amount of 10 mg was the gold standard in ATO cancer therapy. The Examiner then states that the fact that *Zhang* teaches a range of 1-10 mg of ATO suggests that dosage amount other than

10 mgs can be administered to patients in need thereof. Even if one skilled in the art had been motivated to administer ATO in a dosage amount different from 10 mg based on this disclosure, Applicants submit that the collective teachings of the prior art suggest that the dosage would not have been determined based on the weight of the patient.

Lastly, the Examiner concludes that dosing ATO based on body weight would have been obvious "within the language of a 'therapeutically effective dosage'". This is Applicant's own claim language. Thus, the statement is an exercise in impermissible hindsight reconstruction. What is also clear is that the claim limitation of "determining a therapeutically effective dosage amount of arsenic trioxide based upon the weight of a patient," has been ignored.

In view of the foregoing, reconsideration and withdrawal of the rejection based upon *Zhang* are respectfully requested.

In response to the rejection of claims 1-6 as obvious over *Chen*, applicants reiterate the arguments set forth in their prior response. *Chen* reports on *in vitro* studies conducted in order to elucidate the possible cellular and molecular mechanisms of arsenic trioxide on APL patients. In the second paragraph of this publication, *Chen* refers to a report conducted in China showing that administration of 10 mg per day of arsenic trioxide via intravenous infusion for 28-60 days induced clinical complete remission in 65.6% of APL patients, and that 28.2% of patients had a survival of more than ten years. Thus, *Chen* teaches a method of treating APL based on flat dosing of ATO. Once again, each patient was dosed with an identical amount of drug. In the last full paragraph on page 1053, *Chen* makes additional reference to another clinical use of arsenic trioxide in connection with relapsed APL patients, wherein the

drug was administered to eight relapsed APL patients at a dose of 10 mg/day via intravenous drip diluted in 500 mL of 5% glucose saline and administered within two hours. Here again, all eight patients received identical amounts of drug regardless of their weight.

On page 2 of the Action, the Examiner has countered that although *Chen* does not explicitly teach ATO dosing based on body weight, it is obvious within the language of a "therapeutically effective dosage," and that "it is obvious that within the language of a "therapeutically effective dosage", the amount of ATO for treatment has to be determined based on the weight of the body." Basically, this is the same position that the Examiner has taken with respect to *Zhang*. Thus, Applicants' arguments apply equally here. First, inherency is irrelevant in the obviousness determination. Second, the Examiner is improperly relying upon applicants' own claim language as a basis for his rejection. Third, the recitations of the instant claims that require determination of the therapeutically effective dose based on the weight of the patient have been ignored. In sum, *prima facie* obviousness with respect to *Chen* has not been established.

The Examiner has pointed out that *Yang* is being maintained only to reject claim 1. However, there is simply no explanation, one way or the other, as to why this reference is maintained with respect to claim 1. Accordingly, applicants reiterate the arguments set forth on pages 6-7 of the prior response. Specifically, *Yang*'s invention is directed to a method for the preparation of a type of medication that contains arsenic for the treatment of early cervical and skin cancer. There is no disclosure of treating cancer (*e.g.*, leukemia) patients with a therapeutically effective dosage of ATO based on their weight.

According to the disclosure of this patent publication, the primary raw materials in the medication are white arsenic, alunite, realgar, and *Commiphora Myrrha*, with each being present in the medication not only in terms of specific amounts, but specific weight ratios, *i.e.*, 3:4 for the white arsenic and alunite, and 1:2 for the realgar and *Commiphora Myrrha*, and optimum percentages by weight of 18% for the arsenic trioxide and 6% for the aluminum arsenate. On page 6, *Yang* teaches that in order to prepare the medication, each ingredient is pre-pulverized and weighed in accordance with the following weight ratios: White arsenic 30-75; alunite 40-100; realgar 2-8; and *Commiphora Myrrha* 1-4. On page 7, *Yang* teaches even that even better results can be obtained when the ingredients are added in specific weight ratios of 3-4 for the white arsenic and alunite; and a weight ratio of 2:1 for the realgar, and *Commiphora Myrrha*.

On page 8, *Yang* teaches that the medication may be formulated into tablets, bougie, and other formulations using conventional methods. On pages 9-10, *Yang* provides a summary of a study of clinical treatment of 230 patients with early cervical cancer. There is no disclosure, however, as to how these patients were dosed with the medication. Thus, there is no disclosure or suggestion to treat cancer patients with a therapeutically effective dosage of ATO on a weight basis.

On the basis of the foregoing, applicants respectfully submit that none of the cited references would have rendered the claimed invention obvious. The Examiner has failed to establish that the claimed invention would have been *prima facie* obvious to a person skilled in the art. The additional evidence of record, along with other arguments and the Ellison declaration, strongly favor a determination of nonobviousness.

Post-filing reports by third parties evidence a persisting concern over toxicity, even in connection with the weight-based dosing regimens that were under evaluation by then.

For example, the Westervelt group reported the results of another of its studies to determine, in the context of treating relapsed or refractory APL, the maximum tolerated dose or the minimum effective dose of ATO, thereby further to illuminate efficacy at that dose and to delineate the acute and chronic toxicities of ATO. Westervelt, *et al.*, Blood *98(2)*:266-71 (2001)(PTO-1449, page 4, CS2). Once again, the study design entailed a weight-based dosing scheme, this time beginning at a dose of 0.10 mg/kg and increasing in increments of 0.05 mg/kg per day (page 267, left column). The study was curtailed at 0.10 mg/kg per day, however, on account of three unexplained deaths, which the investigators suspected were due to arsenic-related cardiac arrhythmia. The (2001) Westervelt publication concludes with a warning to the effect that the deaths suggest more toxicity, associated with the ATO dosages, than had been recognized previously, and that until these issues were better defined, ATO should be used with caution.

Westervelt, *et al.* concede that their results were in direct contrast with the results achieved in the trial reported in Soignet, *et al.* (2001) (*supra*) from the standpoint of the unexplained deaths. On the right column of page 270, they acknowledge that in the studies reported in *Soignet*, 52 patients were treated without any treatment-related deaths. While proffering various theories to explain the differing results, Westervelt, *et al.* reached no conclusions on this point.

From the viewpoint of *Soignet* (2001), the 3 unexplained deaths reported in *Westervelt* (2001) were simply an anomaly: "Recently, other investigators have reported episodes of nonsustained ventricular tachycardia in patients being

treated with ATO for relapsed APL. Ventricular arrhythmias, other than the episode of torsades discussed above, were not observed in patients on this study, and these events have not been reported by Chinese investigators with clinical experience in using ATO." (page 3859; citations omitted). Applicants submit that *the skilled artisan* would have deemed the results of Applicants' claimed methodology as unexpectedly effective, without the toxicities observed by Westervelt's group.

Overall, the results achieved to date in connection with Applicants' claimed invention are in sharp contrast to the state of the art. For example, in paragraph 11 of his declaration, Dr. Ellison states that since the time of FDA approval for ATO (Trisenox®), data already in the literature have been augmented by the results of treating an additional 2,228 patients with doses of about 0.15 mg/kg per day or greater. To date, these additional results have included no reported deaths attributed to cardiac arrhythmia.

Lastly, as described in ¶12 of his declaration, Dr. Ellison explains that subsequent to the present invention, another group of oncologists chose to modify flat dosing to a dosing based upon the patient's size; this, in recognition of a need to protect patients from toxic doses of ATO during the APL treatment. See Au, *et al.*, Annals of Oncology *14*:752-57 (2003) (copy enclosed). Au *et al.* adopted a BSA dosing scheme, however. Thus, they described the use of BSA dosing in the context of treating a group of patient with relapsed APL. Initial treatment was on a flat-dosage basis for APL patients who underwent bone-marrow transplantation and ATO therapy. For double-relapse patients, however, the dosage was metered to take into account the size of the patient on a surface area basis. The difference in initial dosing and double-relapse dosing can only be interpreted as an acknowledgement of the need to balance

toxicity and efficacy for the patients who had been weakened by extensive therapy beforehand. When faced with the same problem that the present inventors confronted, in other words, Au, *et al.* resorted to more conventional treatment scheme, with dosing based upon patient surface area.

Yet other post-filing publications indicate that the claimed invention can be practiced, safely and effectively, in connection with other cancers. For example, Vey, "*Arsenic trioxide for the treatment of myelodysplastic syndromes,*" in Expert. Opin. Pharmacother. *5(3)*:613-621 (2004)(of record), reports the preliminary results of ongoing Phase II studies conducted in patients with myelodysplasia (MDS) using ATO administered on a weight basis *i.e.*, 0.25 mg/kg/day. The authors conclude that arsenic trioxide is a promising drug with a favorable toxicity profile:

> Arsenic trioxide is an old drug which has recently been rediscovered. The renewed attention on this compound has revealed its wide range of biological activities which support the rationale for its use in MDS, a disease for which no standard treatment has yet been established. The early results of the ongoing clinical studies confirm that arsenic trioxide has a favourable toxicity profile and can be administered on an out-patient basis in the MDS population which involves a majority of elderly patients. As previously reported in patients with APL, most of the adverse effects are non-chemotherapy-like, moderate and regress shortly after cessation of therapy.
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> The efficacy assessment arsenic trioxide in MDS still rely on preliminary reports. However, the results of the different ongoing Phase II studies are consistent and some conclusions can be drawn: arsenic trioxide has clinical activity in MDS; the overall response rate is in the 25 – 30% range; the main clinical benefit is represented by HIs which can be observed across all haematological lineages; durable transfusion-independence can be achieved whereas complete or partial remission are anecdotal. These results thus indicate that arsenic trioxide is a

promising drug for the treatment of MDS. Its favourable toxicity profile encourage the design of combined treatment strategies.

In conclusion, reconsideration and withdrawal of the rejections are respectfully requested.

Claims 1-9 have been rejected under obviousness-type double patenting, as being unpatentable over claims 1-7 of U.S. Patent 6,770,304. The Examiner has concluded that the conflicting claims are not patentably distinct from each other, as follows: "[t]he '304 patent teaches that the dose must be a 'therapeutically effective amount' of ATO which is the same requirement for instant claim 1. The limitation in Applicant's claim 1 (based on the weight of the subject) is obvious within the language of 'a therapeutically effective dose' of the patent claim." Applicants respectfully traverse the rejection.

There is no suggestion in the claims of the '304 patent to determine a therapeutically effective dosage based on the weight of a patient, and thus is not "obvious within the language of 'a therapeutically effective dose' of the patent in claim." The instant claim limitations cannot be ignored. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

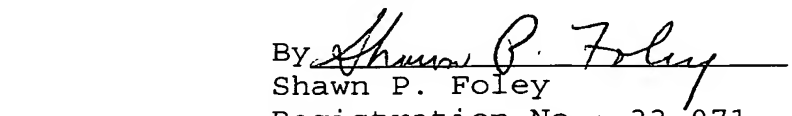
As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefore.

Dated: December 14, 2004

Respectfully submitted,

By 

Shawn P. Foley
Registration No.: 33,071
LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK, LLP
600 South Avenue West
Westfield, New Jersey 07090
(908) 654-5000
Attorney for Applicant

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